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Molecular Defects in the Chondrodysplasias

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There has been a recent explosion of knowledge concerning the biochemical and molecular defects in the skeletal dysplasias. Through both the candidate gene approach and positional cloning, specific gene defects that produce the skeletal dysplasias have been identified and may be classified into several general categories: 1) qualitative or quantitative abnormalities in the structural proteins of cartilage; 2) inborn errors of cartilage metabolism; 3) defects in local regulators of cartilage growth; and 4) systemic defects influencing cartilage development.

KEY WORDS: collagen, skeletal dysplasias, cartilage oligomeric matrix protein, achondroplasia, thanatophoric dysplasia, pseudoachondroplasia, campomelic dysplasia, multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia, achondrogenesis, diastrophic dysplasia, atelosteogenesis, chondrodysplasia punctata, fibroblast growth factor receptor

INTRODUCTION

Based on similarities in their clinical, radiographic, and morphologic findings, the chondrodysplasias were grouped into bone dysplasia families which, Spranger [1985] hypothesized, share common pathophysiological mechanisms. Great progress has been made in the basic biology of collagens and proteoglycans; advances in the human genome initiative have resulted in an explosion of knowledge concerning the biochemical and molecular defects in the skeletal dysplasias which have confirmed Professor Spranger's hypothesis. Through both the candidate gene approach and positional cloning, specific gene defects that cause skeletal dysplasias have been identified and may be classified into several general categories: 1) qualitative or quantitative abnormalities in the structural proteins of cartilage; 2) inborn errors of cartilage metabolism; 3) defects in local regulators of cartilage growth; 4) systemic defects influencing cartilage development; 5) disorders in which the gene has been identified but its pathogenetic mechanism is unknown; and 6) disorders in which, at the time of this writing, the gene has been mapped but not yet identified (Table I).

DEFECTS IN STRUCTURAL PROTEINS OF CARTILAGE

Type II Collagen COL2A1

Since type II collagen is found primarily in cartilage, the nucleus pulposus, and the vitreous humor of the eye, it was postulated that type II collagen defects would be found in those disorders in which these specific tissues were affected [Murray et al., 1989]. Indeed, biochemical and molecular defects in type II collagen have been found in a large group of patients with phenotypes ranging from severe achondrogenesis II, to hypochondrogenesis, to the various spondyloepiphyseal dysplasias and spondyloepimetaphyseal dysplasias, through Kniest dysplasia, Stickler syndrome, and mild spondyloepiphyseal dysplasia (SED) resulting in "precocious" familial osteoarthropathy [Spranger et al., 1994; Rimoin et al., 1994]. These disorders share dominant mutations of the type II collagen gene (COL2A1) and have been called "type II collagenopathies." There appears to be a direct correlation between the ratio of type I to type II collagen in cartilage and the clinical severity of the disorder. Normally, type I collagen is not found in cartilage; however, in most cases of achondrogenesis type II, which is the most severe of these disorders, only type I collagen is seen in cartilage. In hypochondrogenesis, which is less severe radiographically, cartilage contains both type I collagen and posttranslationally overmodified type II collagen. In the SEDs, type I collagen is not seen at all, and both overmodified and normal type II collagen can be found in cartilage.

Mutations which result in a substitution for a triple helical glycine residue appear to be the most common type [Rimoin et al., 1994]. In all cases of achondrogen-

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

Table I. Molecular Defects in the Chondrodysplasias

Gene	Disorder
Structural proteins of cartilage	
COL2A1	Achondrogenesis II
	Hypochondrogenesis
	SED
	SEMD
	Kniest
COL9A2	MED
COL10A1	MD Schmid
COL11A2	Stickler
	OSMED
COMP	Psuedoachondroplasia
	MED
Inborn errors of cartilage metabolism	
DTST	Achondrogenesis IB
	Atelosteogenesis II
	Diastrophic dysplasia
ARSE	Chondrodysplasia punctata XR
Lysosomal enzymes	Mucopolysaccharidoses
	Mucolipidoses
Local regulators of cartilage growth	
FGFR3	Achondroplasia
	Hypochondroplasia
	Thanatophoric I and II
PTH-PTHRP receptor	Metaphyseal dysplasia, type Jansen
Systemic defects influencing cartilage development	
Peroxisomal defects	Rhizomelic chondrodysp. punctata
ADA deficiency	Combined immuno. deficiency
Gene identified, mechanism unknown	
SOX9	Campomelic dysplasia
EXT1	Multiple exostoses 1
Gene mapped, not yet identified	
	Cleidocranial dysplasia
	Ellis van Creveld
	Trichorhinophalangeal 1 and 2
	Pycnodysostosis
	Multiple exostoses 2 and 3

esis II/hypochondrogenesis in which mutations have been defined, there are single amino acid substitutions for a glycine residue in the type II collagen helix, all of which are clustered toward the carboxyl terminal end of the molecule. In the SEDs and spondyloepimetaphyseal dysplasias (SEMD), a variety of single nucleotide substitutions has been described throughout the molecule, in addition to deletions and insertions. Kniest dysplasia appears to be somewhat unique in primarily having exon-skipping mutations clustered around the amino terminal end of the molecule [Bogaert et al., 1994; Wilkin et al., 1994]. Only one or two exceptions to this rule have been found. In Stickler syndrome, approximately half of the families show linkage of the phenotype to the COL2A1 locus, and all of the type II collagen gene mutations that have been identified have resulted in stop codons, presumably leading to decreased synthesis of type II collagen [Ritvaniemi et al., 1993]. Thus, mutations which result in the synthesis of qualitatively abnormal type II collagen chains lead to more severe phenotypes, whereas mutations that result in reduced synthesis of structurally normal type II collagen produce the milder Stickler phenotype.

Type IX Collagen COL9A2

Some families with multiple epiphyseal dysplasia, Fairbanks type, have been found to be linked to the COL9A2 gene [Briggs et al., 1994], and mutations have now been defined in these cases. Phenotypic differences between the multiple epiphyseal dysplasia (MED) cases with COL9A2 mutations and those with cartilage oligometric matrix protein (COMP) mutations (see below) have yet to be identified.

Type X Collagen (COL10A1)

Mutations in COL10A1 have been defined in Schmid-type metaphyseal dysplasia [Warman et al., 1993; McIntosh et al., 1995]. All of the mutations identified to date have been in the region of the gene which encodes the carboxyl-terminal chain association domain, and presumably lead to a reduced amount of type collagen in the matrix. The metaphyseal abnormalities seen in this condition correlate with the presence of type X collagen found exclusively in the hypertrophic zone of the growth plate. However, other forms of metaphyseal dysplasia do not have mutations in this molecule.

Type XI Collagen (COL11A2)

A mutation has now been described in COL11A2 in a family with Stickler syndrome [Vikkula et al., 1995]. The phenotype appears to be distinct from the Stickler cases that result from type II collagen defects in that they do not have the severe myopia and vitreoretinal degeneration found in the type II collagenopathies. This is consistent with the fact that COL11A2 is not expressed in the vitreous humor. In addition, homozygosity for a mutation in COL11A2 has been found in a family with ostospondylyomegaepiphyseal dysplasia (OSMED) [Vikkula et al., 1995].

Cartilage Oligomeric Matrix Protein (COMP)

Cartilage oligomeric matrix protein is encoded by a gene on the short arm of chromosome 19, where the pseudoachondroplasia phenotype was mapped. A variety of mutations has now been defined in the COMP gene in pseudoachondroplasia, and in a number of cases of multiple epiphyseal dysplasia [Briggs et al., 1995; Hecht et al., 1995b]. COMP is a member of the thrombospondin family of extracellular calcium-binding proteins, and the mutations appear to occur frequently in the calmodulin-like repeat region of the molecule. Further studies will be required to identify the differences between mutations that produce the pseudoachondroplasia and MED phenotypes.

INBORN ERRORS OF CARTILAGE METABOLISM

Diastrophic Dysplasia Sulfate Transporter (DTDST)

Diastrophic dysplasia was mapped to the long arm of chromosome 5 by linkage disequilibrium mapping, and subsequently Hästbacka et al. [1994] identified a gene

at this locus that closely resembled a sulfate transporter gene previously described in the rat. Abnormal sulfate transport was demonstrated in vitro, and decreased proteoglycan sulfation was detected in patient cartilage. Reduced sulfate transport appears to have a dramatic effect on sulfation of chondroitin sulfate-containing proteoglycans, a family of highly expressed and heavily sulfated proteins that participate in the function of cartilage in supporting compressive loads. Although DTDST is also expressed in other tissues, cartilage is hypothesized to be disproportionately affected by DTDST mutations, primarily due to its high demand for sulfate and its avascular nature. A number of mutations in the DTDST gene have been described in both Finnish and non-Finnish patients with this disorder [Hästbacka et al., 1996].

Superti-Furga [1994] described similar defects of in vitro sulfate uptake in a more severe disorder, known as achondrogenesis 1B. Based on these data and similar morphological characteristics of cartilage in the two disorders and a third disorder, atelosteogenesis type II (i.e., rings of collagen around the chondrocytes), mutations in DTDST were sought in achondrogenesis type IB and atelosteogenesis type II. DTDST mutations were identified in both conditions, demonstrating a series of allelic phenotypes of variable severity [Superti-Furga et al., 1996; Hästbacka et al., 1996]. Achondrogenesis IB appears to have mutations in the coding regions on both chromosomes, mainly representing early stop codons. Atelosteogenesis II also has mutations in the coding regions of both chromosomes, but with less severe changes, i.e., late dysplasia patients have had two mutations in the coding region to date. Thus, there appears to be some genotype-phenotype correlation, with the most severe disease, achondrogenesis IB, due to mutations resulting in a null phenotype, 2nd with atelosteogenesis II resulting from a partial loss of function; in diastrophic dysplasia, the clinically mildest of the disorders, there is somewhat more transporter activity.

Arylsulfatase (ARSE)

The X-linked recessive form of chondrodysplasia punctata was mapped to the short arm of the X chromosome (Xp22.3), near the boundary of the pseudoautosomal region close to the steroid sulfatase locus. Franco et al. [1995] identified three adjacent genes which encoded previously unrecognized enzymes of sulfate metabolism in this region of the chromosome, which were named arylsulfatase D, E, and F. Missense mutations in the ARSE gene were found in a number of boys with X-linked recessive chondrodysplasia punctata, but clearly not in all of them. It was speculated that mutations in ARSD or ARSF genes might be responsible for the other cases.

Other Lysosomal Enzyme Defects

Although beyond the scope of this review, it should be mentioned that mutations in a number of genes coding for a variety of lysosomal enzymes have been described in the mucopolysaccharidoses and mucolipidoses, which produce a dysostosis multiplex form of skeletal dysplasia [Neufeld and Muenzes, 1995].

LOCAL REGULATORS OF CARTILAGE GROWTH

Fibroblast Growth Factor Receptor 3 (FGFR3)

In 1994, the achondroplasia gene was mapped to the short arm of chromosome 4 (4p16.3), close to the Huntington disease locus [Le Merrer et al., 1994a; Francomano et al., 1994]. During the long search for the Huntington disease gene, a gene that later became a candidate for the achondroplasia disease gene was identified, i.e., fibroblast growth factor receptor 3 (FGFR3). Within a few months of the linkage report, mutations in FGFR3 were found to be responsible for achondroplasia [Shiang et al., 1994]. Of great interest was the finding that over 98% of the cases analyzed were due to the same amino acid substitution (Gly380Arg). Almost all of the cases carried the same mutation, a G to A transition at nucleotide 1138, and the remaining cases had a G to C transversion at the same nucleotide, resulting in the same single amino acid substitution. Since over 80% of cases of achondroplasia represent new mutations, this represents the single most frequent mutation known in humans.

A number of mutations in FGFR3 have now been found in thanatophoric dysplasia (TD) [Tavormina et al., 1995]. Individuals with thanatophoric dysplasia, type II, with straight femora and severe cloverleaf skull, all had the same mutation, resulting in a Lys650glu substitution in the intracellular tyrosine kinase domain of the receptor. In cases of TD I, which is characterized by curved femora, with or without cloverleaf skull, most of the mutations were found in the extracellular domain, and sharing a substitution of a cysteine for another amino acid, e.g., Arg248cys, Ser249Cys, Ser371Cys, or Tyr373Cys. Rousseau et al. [1995] have also described mutations in a stop codon (807) in 5 patients with TD I.

Heterozygosity for FGFR3 mutations has also been detected in hypochondroplasia. In 8 of 14 alleles studied by Bellus et al. [1995a], a C1620A transversion that causes an Asp540Lys substitution was described. Subsequently, a second mutation at the same nucleotide, C1620G, which predicts the same amino acid substitution (Asp540Lys), was found in a proportion of cases [Bellus et al., 1995b].

Parathyroid Hormone-Related Peptide PTHrP Receptor

Jansen-type metaphyseal chondrodysplasia is an autosomal-dominant skeletal dysplasia with ricketic-like changes in the metaphyseal areas of the bones [Schipani et al., 1995]. A mutation has been defined in the parathyroid hormone-related peptide PTHrP receptor. Patients were heterozygous for the mutation, which caused a histidine to arginine substitution at position 223 in the PTHrP receptor protein.

SYSTEMIC DEFECTS INFLUENCING CARTILAGE DEVELOPMENT

Peroxisomal Defects

A variety of defects in peroxisomal function has been described in patients with the autosomal-recessive rhizomelic form of chondrodysplasia punctata (RCDP) [Heikoop et al., 1992]. Deficiency of activity of peroxiso-

mal enzymes and elevated plasma phytanic acid concentrations have been described in a large number of cases with the specific rhizomelic form, but not in any of the other forms of chondrodysplasia punctata. Moser et al. [1995] have described 16 complementation groups in patients with disorders of peroxisomal assembly. Those with the RCDP phenotype belonged to a single complementation group.

Adenosine Deaminase (ADA) Deficiency-Combined Immunodeficiency Disease

ADA deficiency can result in metaphyseal dysplastic changes, especially noteworthy in the costochondral junctions [Ratech et al., 1985]. The histopathological changes at the growth plate are distinct from those observed in the other metaphyseal dysplasias. These skeletal changes regress following bone marrow transplantation.

GENE IDENTIFIED BUT MECHANISM UNKNOWN

SOX 9

Campomelic dysplasia of the classic long-bone variety is one of many disorders associated with sex-reversal. A substantial number of XY individuals have genital abnormalities that range from minor abnormalities of the external genitalia to complete sex reversal. Chromosomal rearrangements in cases of campomelic dysplasia localized the responsible gene to 17q24.1–q25.1 [Tommerup et al., 1993]. High-resolution mapping of the candidate region positioned a breakpoint in one patient close to the SOX9 locus. SOX9 is a transcription factor gene structurally related to the SRY (sex-determining region Y gene), which encodes the factor necessary for testicular development in mammals [Foster et al., 1994]. Mutations of SOX9 have now been reported in a number of patients with classic campomelic dysplasia who are chromosomally normal. They were found in 46,XX and 46,XY females, as well as in 46,XY male. All patients described to date were heterozygous for their mutations, negating the previously proposed autosomal-recessive inheritance pattern for this disorder. Thus, campomelic dysplasia of the classic type appears to be an autosomal-dominant disorder. The gene is expressed in condensing mesenchyme, but not in mature chondroosseous tissue.

Multiple Exostoses (EXT) and Trichorhinophalangeal (TRP) Syndromes

Hereditary exostoses (EXT) is an autosomal-dominant disorder that has been shown to be heterogeneous on molecular grounds with different chromosomal locations identified on chromosomes 8, 11, and 19 [Le Merrer et al., 1994b; Hecht et al., 1995a]. The multiple exostosis gene on chromosome 8 (ext1) has been isolated, but its function is still unknown. Trichorhinophalangeal syndrome II appears to be a contiguous gene syndrome on chromosome 8, probably including the multiple exostoses gene [Ludecke et al., 1995].

GENES MAPPED BUT NOT YET IDENTIFIED

At the time of this writing, the map location of the genes for a number of other skeletal dysplasias had been described, but the responsible gene has not yet been identified (Table I). Identification of these and other genes responsible for the skeletal dysplasias will likely be accomplished in rapid fashion. Our next task will be to define the function of each of the aberrant proteins, and to develop mechanisms to replace or bypass the specific defect in each condition.

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